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NEUROLOGICAL COMPLICATIONS OF ADDICTION TO HEROIN*

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ALTHOUGH addiction to heroin is a major public health hazard and is the leading cause of death in New York City in the 15- to 35-year age group, the neurologic complications have been recognized only recently.[1, 2] This study will outline the clinical classification of the neurological complications of addiction to heroin (Table I) and will correlate these observations with neuropathological studies made at the Office of the Chief Medical Examiner of New York City. The clinical entities described in this study were observed at the Harlem Hospital Center, which is a 1,000-bed municipal institution serving the central Harlem area, where more than 10% of the adults admitted to the medical services are heroin addicts. This figure reflects the extraordinary rate of addiction in this Harlem area, where it is estimated that more than 50,000 addicts may be obtaining their supplies of heroin daily.

Heroin mixtures are presently sold in central Harlem in $2, $3, and $5 packets weighing about 100 mg.; these may contain 10 to 15% heroin. These packets usually also contain 20 to 25% quinine. The remainder consists of lactose, powdered milk, mannitol, fruit sugars, or other adulterants. The precise etiologic factor or factors leading to the neurological complications of addiction to narcotics are difficult to assess because of the complexity of the crude unsterile mixtures taken and the methods by which they are administered.

TABLE I. CLASSIFICATION OF THE NEUROLOGICAL COMPLICATIONS OF ADDICTION TO HEROIN

I. Noninfectious neurological complications
- Cerebral complications of heroin "overdose"
  - Coma without complications
  - Coma with neurologic sequelae
    - Seizures (focal, generalized, status epilepticus)
    - Increased intracranial pressure
    - Acute delirium
    - Chronic organic brain damage
    - Delayed postanoxic encephalopathy
    - Cerebral vascular accident
    - Involuntary movement disorder
    - Deafness
  - Toxic (quinine) amblyopia
  - Transverse myelitis
  - Peripheral nerve lesions
    - Brachial and lumbosacral plexitis
    - Atraumatic and traumatic mononeuropathy
    - Acute and subacute polyneuropathy
  - Muscle disorders
    - Acute rhabdomyolysis with myoglobinuria
    - Chronic myopathy
    - Crush syndrome and other muscle damage

II. Infectious and postinfectious neurological complications
- Cerebral complications of endocarditis and other septic states
- Local abscesses with nerve or muscle involvement
- Cerebral complications of hepatitis
- Tetanus

In several categories described in this study (transverse myelitis, plexitis, and acute rhabdomyolysis) we have observed that the complication may arise in a patient who has recently become reexposed to heroin after a period of abstinence from the drug. This phenomenon was observed even in patients who had taken a single injection after a drug-free period. Similar complications have been observed, however, in patients who have been continuously exposed to adulterated heroin. We surmise tentatively that some of the neurological complications may be caused by an allergic reaction to the heroin-adulterant mixture. The recent demonstration by Kilcoyne et al.[3] of immunoglobulin and

complement in the kidneys of heroin addicts who had developed the nephrotic syndrome "may implicate heroin addiction as an infectious, toxic or immunological stimulus which may be expressed as a neuritis or vasculitis or as the nephrotic syndrome."[3] This concept warrants further extensive study.

Noninfectious Neurological Complications

Cerebral Complications of Heroin "Overdose"

A large number of heroin addicts sooner or later suffer one or more episodes of "overdose." Although overdoses sometimes result from deliberate suicidal attempts or from deliberate homicide by a distributor, in most cases overdoses are accidental. The uncomplicated overdose of heroin corresponds to overdosage of other opium alkaloids; coma, depressed respiration, increased pulse rate, and contracted pupils are the main symptoms. More than 10 cases of overdose are treated weekly in the emergency room at Harlem Hospital. Most of these patients have mild reactions and are discharged directly from the emergency room. Only patients who have severe, prolonged coma or other complications are admitted.

A review of 42 case histories of patients admitted to Harlem Hospital with the diagnosis of overdose of heroin showed that 11 had associated pulmonary edema (one died); six, pneumonia; two, hepatitis (one died); two, asthma attack (in direct relation to the injection); and four had epileptic seizures.[2] Lumbar punctures performed in 12 of these patients showed that seven had increased cerebrospinal fluid pressure (200 mm. of H_2O or more). Increased intracranial pressure was found in all three patients with pulmonary edema who received a lumbar puncture but only in one of three with pneumonia.

This study illustrates that convulsive seizures and increased intracranial pressure may complicate overdosage with heroin. Convulsive seizures may occur acutely and are usually of the grand mal type. We have also seen acute episodes of focal seizure in which focal cerebral lesions were not demonstrated. These convulsive seizures stop at the time of recovery from the overdose, and repeated attacks did not occur in those patients whom we were able to follow over a longer period of time.

Increased intracranial pressure is rather common during overdosage and occurs often in connection with pulmonary edema. It is unclear if

there is a cause-and-effect relation between these conditions. This corresponds well with the neuropathological findings: about 60% of patients dying of acute heroin reactions have demonstrable cerebral edema.[4, 5] The pathogenesis of pulmonary edma[6] as well as cerebral edema is unknown and is an area where special studies would be of importance for improving treatment. Drs. Reichman, Shim, Baden, and Richter have recently studied the acute effects of street heroin in addicted and nonaddicted baboons.[7] Animals became markedly hypoxic and hypercapneic for several hours but failed to develop pulmonary edema. The degree of respiratory depression was similar to that seen in man.

Cerebral sequelae may occur after an overdose.[1, 2] Basic data in this area are very limited at present; many of the cerebral changes may be due to anoxia. Following reaction from a severe overdose the patient may pass through a phase of acute delirium, with agitation, tremors, and hallucinosis lasting from several hours to several days. The delirium rarely heralds the onset of chronic organic cerebral dysfunction. We have observed three cases of dementia following overdose. This chronic brain-damage syndrome probably was caused by anoxia in connection with the overdose although none of these patients suffered cardiac arrest. We have also observed two patients with cardiorespiratory arrest following overdose who developed signs of delayed postanoxic encephalopathy.[8]

At Harlem Hospital we have recently examined four patients who had cerebral vascular accidents following overdosage with heroin. In these patients there was no evidence of embolism. The neurological deficit in each became evident when he awoke from coma. Angiograms did not reveal evidence of vasculitis but occlusion of branches of the middle cerebral artery was demonstrated in two instances. We have observed a 31-year-old man who, on awakening from an overdose, had a fully developed unilateral Parkinsonian syndrome which has persisted on one side for five years. Another 28-year-old man on awakening from an overdose had left-sided hemiballistic movements, which resolved incompletely during a period of five weeks. These disorders of involuntary movement may also be of vascular origin, but proof is lacking. We have observed a single case of bilateral deafness occurring after overdosage. Whether this symptom was due to anoxia or was a direct toxic effect is not known.

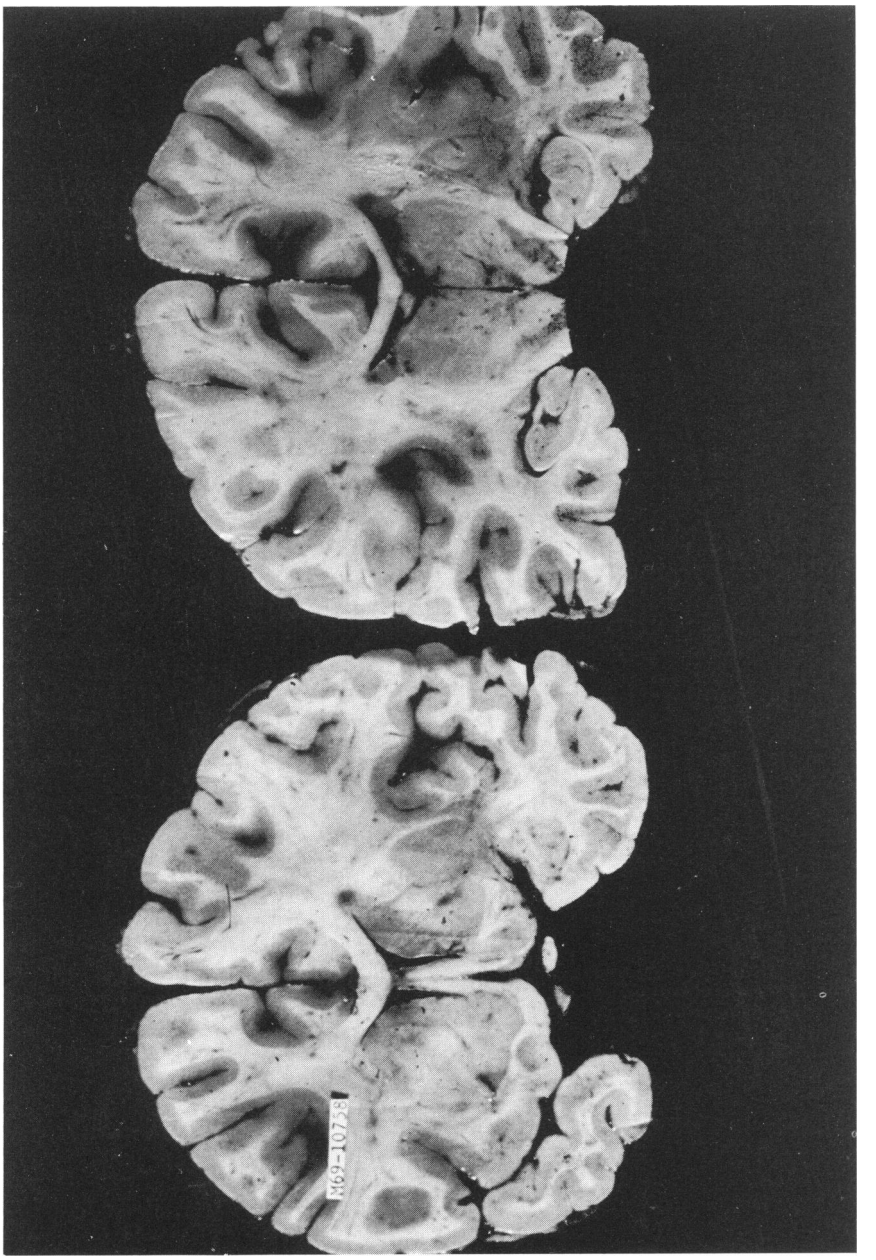

Fig. 1. Diffuse swelling of the cerebral hemispheres with gyral flattening and ventricular compression in a case of acute reaction to heroin.

Addicts who died during acute reactions have shown a high incidence of cerebral edema. Pearson[5] found cerebral edema in 17 of 21 cases, with gross diffuse swelling of the cerebral hemispheres with gyral flattening, uncal grooving, and ventricular compression (Figure 1). There was clasmatodendrosis of the astrocytes in the deep white matter with relative arcuate preservation. In some cases swelling of astrocytes was observed at the periphery of the zone of clasmatodendrosis. Degeneration of myelin has not been a feature of these acute cases but was seen after delayed death related to "overdose." In three of the 21 patients who died of acute reactions, bilateral cystic lesions were found in the globi pallidi. Although such cysts have been observed intermittently[9] in the more than 1,200 cases of death in heroin addicts now examined yearly at the Office of the Medical Examiner of New York City, the high incidence in this series is probably fortuitous.

Clinical experience would indicate that hypoxia and hypercapnia may play an important role in the development of cerebral edema as well as in the other acute cerebral lesions that we have seen. Similar patterns of brain damage have been observed in acute hypoxemia from other causes.[10] Morphine has a direct toxic effect on cells in tissue culture and causes morphologic alterations.[11] The role of cellular toxicity of injected materials in producing the brain lesions which we have described remains undetermined. Other noninfectious changes include infarction of the pituitary gland. The necrotizing angiitis described in amphetamine abusers,[12, 13] some of whom also used heroin, was not seen in our material.

Toxic (Quinine) Amblyopia

Blindness, considered secondary to quinine added to heroin, was first reported a year ago.[14] The patient was taking about 5 gm. of quinine per day. His vision recovered partially while he was not using "street" heroin and did not deteriorate when he resumed the use of heroin unadulturated with quinine. Recently he went back to taking heroin mixed with quinine and his vision deteriorated additionally.

Quinine was first added to some preparations of heroin in the 1930s because of its antimalarial properties but became widely used as an adulterant in the late 1940s because of its bitter taste, which helped to disguise the often diluted quantities of the heroin present. (Heroin is bitter, also, and an addict will customarily taste a sample of what he is

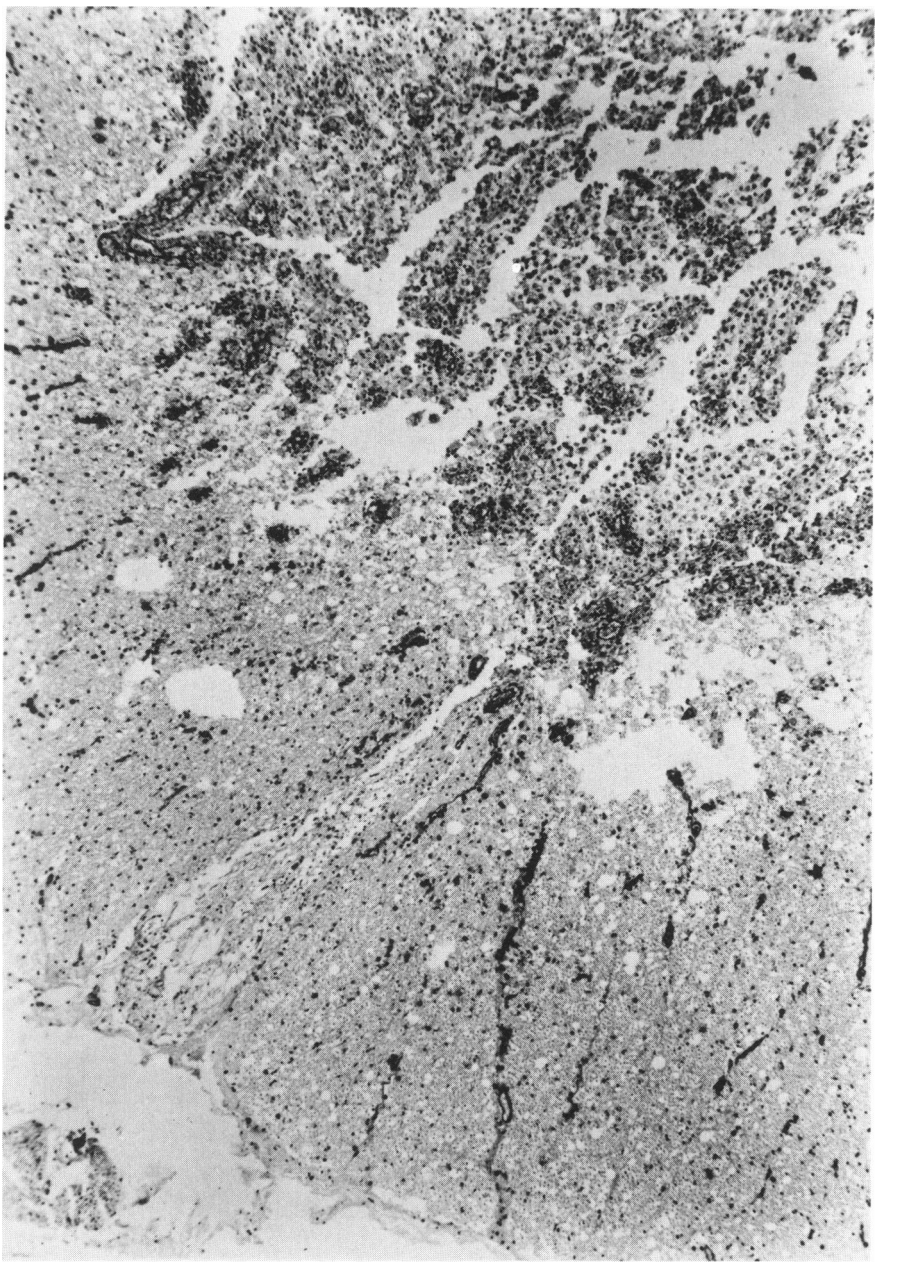

Fig. 2. Thoracic spinal cord (×55) at T-10 level. Necrotic tissue replaced by lipid-laden phagocytes.

buying). In addition, many addicts assert that quinine provides the initial flush or "high," which may result from peripheral vasodilation.

Quinine is a tissue poison[15] and can affect the central nervous system, the heart, the skeletal and smooth muscles, the gatrointestinal tract, the kidney, the blood, the ear, and the eye. It is possible that other toxic reactions seen in addicts may also result from the quinine adulterants.

Transverse Myelitis

Acute transverse myelitis involving thoracic segments was first observed at Harlem Hospital as a complication of addiction to heroin.[16] Three of the initial four patients had not taken heroin for periods of one to six months. The acute myelitis developed shortly after heroin was again taken intravenously. At onset, three patients suddenly became paraplegic, and moderate paraparesis developed in one. All four demonstrated thoracic sensory levels. Myelograms were normal for the three patients on whom they were performed. One patient died five weeks after onset of paraplegia. Extensive necrosis of the spinal cord in the lower thoracic region was found at necropsy (Figure 2). A second patient of the initial series had residual paraparesis and died five years after the onset of symptoms. Old necrosis of the spinal cord gray matter from C-7 to T-8 with cystic changes between C-8 and T-4, minimal damage to the long white tracts, and degenerative changes in dorsal root ganglia were noted.[17]

Eleven cases of transverse myelitis complicating addiction to heroin have now been diagnosed clinically at Harlem Hospital and four cases have been reported from other institutions.[18-20] Three heroin addicts recently seen at Harlem Hospital, with myelitis but with coincident infection (tuberculosis meningitis, tuberculous osteomyelitis of the spine, and pneumococcal meningitis), are not included with these 11 patients, in whom no underlying disease could be found. Four of the 11 have died of causes not directly related to the lesions in the thoracic spinal cord: pulmonary embolism, renal infection, and acute reaction to narcotics. Four survivors have moderate-to-severe paraparesis with thoracic sensory levels, two have mild residual paraparesis, and one recovered completely.

We can only speculate as to what produced the thoracic lesions in our patients. It is possible that a severe systemic reaction to the heroin, quinine, or other adulterants led to temporary vascular insufficiency in

the vulnerable circulation in the thoracic cord. Hypersensitivity reactions or even direct toxic effect of the drugs should also be considered.

Peripheral Nerve Lesions

A variety of peripheral nerve disorders have been documented among heroin addicts at Harlem Hospital.[21] Parenteral injections of many other substances, most notably heavy metals and other toxins, various vaccines,[22] and sera[23] may produce a spectrum of neuritides, among which are polyneuropathy, plexitis, and occasionally mononeuropathy. In addition to an anatomic correspondence, these neuritides have in common with those we have described their occurrence remote from the site of injection and the predilection for radial mononeuropathy and brachial plexitis. Although a variety of neuritides may occur as postinfectious complications,[24, 25] infection was not a prominent finding in our patients with neuropathy. Wherever possible the history of addiction to heroin (length and dose) was checked carefully with the patient's relatives or friends. Patients with concurrent crush injury, local infections, or other medical complications, such as diabetes mellitus, collagen-vascular disease, porphyria, and exposure to toxins such as alcohol, were excluded from this study.

The incidence of plexitis and mononeuritis in heroin addicts far exceeded that seen in unaddicted patients. The hypothesis that a relation may exist between addiction to heroin and certain peripheral nerve disorders will be presented elsewhere, with a statistical analysis of case material.

Lesions which may underlie the clinical neuropathic syndromes have been observed infrequently. This may be partially accounted for by the fact that there have been few biopsies or autopsies on subjects known to be suffering from these complications. Vasculitis is not a feature of heroin addicts observed in New York City. Localized reduction in blood supply to nerves based on such a process was not documented in our present material. A sural nerve biopsy from a patient with severe peripheral neuropathy, apparently related to heroin, showed marked loss of large-caliber axons and their myelin sheaths with continuing active degeneration. Occasionally small foci of chronic inflammation have been observed which were related to peripheral nerves or were in sensory ganglia. More frequently degenerative changes evidenced by residual nodules and neuronophagia are observed in dorsal root ganglia.

The possibility of damage mediated by immunoglobulins, such as that involved in the early stage of experimental allergic neuritis, is not excluded.[26, 27]

Brachial and lumbosacral plexitis. Brachial or lumbosacral plexitis was observed to occur with slow onset, without relation to one specific injection, and without apparent fluctuation after subsequent injections. Intense neuritic pain resembling causalgia frequently was the presenting complaint and mimicked septic arthritis. Weakness and sensory deficit were usually mild to moderate. Electrodiagnostic studies in 13 cases proved the presence of denervation where weakness was minimal and sensory loss inconsistent. We have observed a preponderance of brachial lesions over lumbosacral plexus lesions. Crush or pressure effects on the brachial or lumbosacral plexus and injections directly into axillary or inguinal veins were ruled out by the patients' histories. Plexitis was seen in some instances in association with other heroin-related neurological abnormalities such as transverse myelitis, acute rhabdomyolysis, and chronic myopathy.

Atraumatic and traumatic mononeuropathy. The most frequent neuropathic complication in our experience was atraumatic mononeuropathy. Patients with this complication gave a history of painless weakness begining two to three hours after intravenous injection, which usually was remote from the affected extremity. Usually there was no history of sleep following injection, as would be found in "Saturday night palsy" or pressure neuropathy. Electrical studies showed generalized slowing in the nerves tested rather than in focal areas, such as might follow the injury of a nerve by pressure.

With direct traumatic lesions the history is usually clear. Immediate pain or paresthesias occur in a discrete nerve distribution during the injection of heroin-adulterant mixture. Weakness and sensory deficit may be noted immediately or during attempted activity a few minutes later. Loss of function is usually permanent.

Acute and subacute polyneuropathy. Fulminating symmetrical polyneuropathy resembling the Guillain-Barré syndrome was observed as a life-threatening disease in three heroin addicts. Other cases showed the rapid onset of symmetrical paralysis. Three patients with subacute polyneuropathy had histories of long-standing heroin addiction; two patients had been addicted a year or less. These patients either presented with symptomatic asymmetrical weakness of moderate severity or were rec-

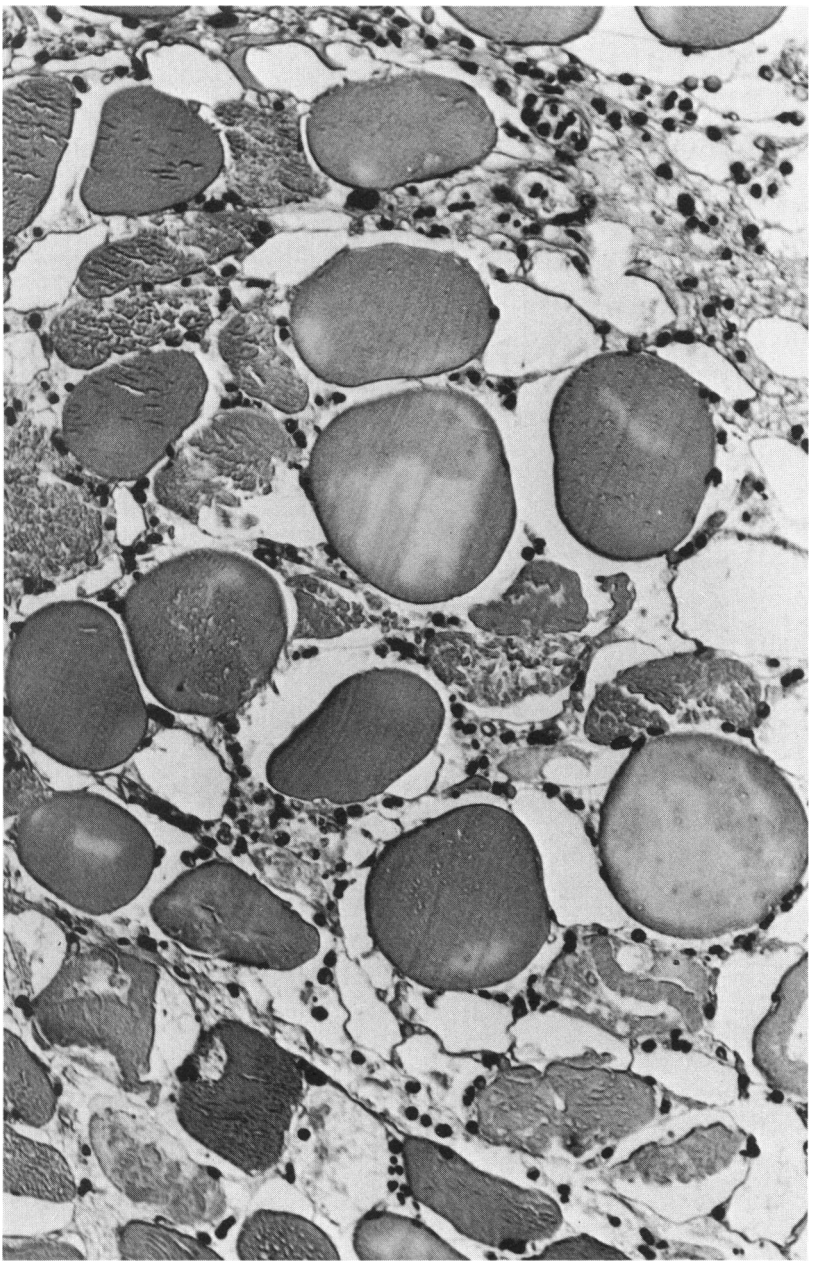

Fig. 3. Cross section of right gastrocnemius muscle showing severe necrosis of all fibers and variable swelling of muscle fibers with contained floccular and homogenized sarcoplasm. Many fibers are completely lysed and there is slight interstitial inflammation. Hematoxylin-eosin, ×63.

ognized to have polyneuropathy while under treatment for other incidental conditions. Only mild weakness was noted in the latter instances.

Muscle Disorders

Several types of muscle involvement will be described which may be seen in users of heroin.

Acute rhabdomyolysis with myoglobinuria. A new syndrome of acute generalized rhabdomyolysis associated with the intravenous injection of adulterated heroin has been reported recently.[28] In these patients we found no evidence of trauma, compression, or ischemia. Myoglobinemia and myoglobinuria were detected by a specific immunologic method.[29] The acute myopathy occurred both with and without renal failure. Generalized muscle tenderness, edema, and profound weakness of all extremities were noted. Complete diagnostic study included electrodiagnostic examinations and muscle biopsies.

Muscle-biopsy specimens presented a spectrum of changes ranging from structural alterations of fibers without necrosis, through necrosis of randomly scattered individual muscle fibers to devastating necrosis of all fibers with severe edema and focal hemorrhage (Figure 3). The inclusions described in one of our cases had the morphological and histochemical characteristics of tubular aggregates. It has been suggested that such aggregates have a detoxifying function since similar structures appear in liver cells of experimental animals exposed to alcohol and barbiturates.[30, 31] There is also evidence, however, which suggests that tubular aggregates may be found in myopathic conditions independent of toxic mechanisms. We are unable to say whether the necrosis observed is due to a direct toxic effect of, or an allergic response to, a component of the complex adulterated heroin mixtures used by addicts. It would thus be premature to speculate on mechanisms of damage at a cellular level.

Chronic myopathy. A fibrosing myopathy is rather common among long-term habitues who use the subcutaneous route of injection. It is a chronic disease caused by the innumerable intramuscular injections of heroin and its adulterants. The gradual obliteration of veins after prolonged addiction may lead to development of brawny edema. This edema both predisposes to, and is reinforced by, episodes of cellulitis and myositis.[32] The myositis may also be a chemical toxic effect of direct intramuscular injection. Chronic subcutaneous and intramuscular

infection may also predispose to chronic muscle changes.[33] The first description of chronic fibrosing myopathy of this nature was of patients who abused meperidine.[32] The disease has similarities with the needle myopathy described by W. K. Engel as well as with the local changes which are seen at the places of injection in patients who have taken drugs intramuscularly for a long time.

Electromyography shows areas completely devoid of electrical activity mixed with myopathic areas. The myopathy is not progressive unless repeated trauma continues.

Crush syndrome and other muscle disorders. Schreiber et al. have outlined the clinical features of crush syndrome complicating overdosage with narcotics.[34] Penn et al. have described similar changes in comatose patients after drug ingestion or injection.[35] At Harlem Hospital we have also observed similar cases of localized compression of limbs in heroin addicts after a period of unconsciousness. A number of other addicts who had experienced no loss of consciousness were noted to have massive swelling limited to the extremity into which heroin had been injected, either deep in the subcutaneous tissues or into muscles. Infection or deep venous thrombosis was ruled out by surgical exploration in two such cases. A toxic or acute allergic reaction was suspected.

Infectious and Postinfectious Neurological Complications

The abuse of narcotics usually involves the intraveous, subcutaneous, or even intramuscular injection of a variety of unsterile substances through makeshift apparatus. The wide variety of infectious complications seen in addicts has been reviewed extensively.[36-40] Let us summarize some recent personal experiences with the central nervous system manifestations of these infections.

Cerebral Complictions of Endocarditis and Other Septic States

During 1971, 17 heroin addicts who had endocarditis were admitted to Harlem Hospital. *Staphylococcus aureus* was the most common organism recovered, and *Candida tropicalis* was isolated from the blood of one patient. Four of these 17 patients had severe involvement of the central nervous system. Two developed bacterial meningitis, one with focal signs suggesting abscess; both died. One patient developed meningitis with hemiparesis and aphasia. He died seven weeks after admission

following subarachnoid hemorrhage presumably caused by rupture of a mycotic aneurysm. One patient had sudden right hemiparesis without meningitis and survived.

Septic states without evidence of endocarditis may also lead to bacterial meningitis, brain abscess, and subdural and epidural abscesses. An addicted patient admitted to Harlem Hospital with pneumococcal meningitis developed, two days after admission, flaccid quadriplegia and urinary and fecal incontinence. Myelograms showed complete block at the second cervical vertebra; and at operation an epidural abscess was found. Drainage failed to relieve the symptoms, and the patient died soon afterward. Another addict recently autopsied at the Office of the Chief Medical Examiner had numerous skin abscesses and had necrosis of the cervical and upper-thoracic spinal cord secondary to a widely extending spinal epidural abscess from which staphylococcus aureus was cultured.

The high-incidence rate of tuberculosis in Central Harlem is reflected among the heroin addicts admitted to Harlem Hospital. Three of 29 patients with tuberculosis meningitis recently treated at Harlem Hospital were heroin addicts.[41]

Falciparum malaria frequently accompanied by acute cerebral lesions was reported by Helpern as rampant among addicts to heroin during the 1930s.[42] No artificially transmitted malaria has been reported in intravenous addicts in New York City since 1943.[43] *Plasmodium vivax* malaria in addicts probably transmitted by servicemen returned from Southeast Asia was reported in 1971 from Bakersfield, Calif. The drug mixtures analyzed there did not contain quinine.[43]

Local Abscesses with Involvement of Nerve or Muscle

Extension of deep subcutaneous infections in the heroin addict may cause direct peripheral nerve or muscle damage. We have rarely observed irreversible peripheral nerve lesions after such involvement. The muscle infections may also lead to permanent fibrotic changes.[32, 33] More than five heroin addicts are admitted each month to Harlem Hospital for treatment of such deep-seated infections.

Cerebral Complications of Hepatitis

Acute viral hepatitis related to use of contaminated needles was the leading cause for admission of heroin addicts to Harlem Hospital be-

tween 1968 to 1971. Of 422 admitted during this period 19 died after a fulminating course. These 19 patients typically experienced rapid onset of hepatic coma, seizure phenomena, and decerebrate rigidity, and died usually two to eight days after admission.

Tetanus

From 1964 through 1971, 34 patients were treated for tetanus at Harlem Hospital by members of the departments of neurology, medicine, anesthesiology, and surgery. Thirty patients were heroin addicts with multiple sites of infection; of these, nine survived. Three of the four nonaddicts survived tetanus. All addicts, even those admitted with mild or moderate symptoms, rapidly progressed to severe tetanus. Nineteen patients were curarized and maintained on a volume-controlled respirator; five of them survived. The rest received varying combinations, usually of phenobarbital, chlorpromazine, morphine, diazepam, and paraldehyde. Except for two patients treated during 1964, control of tetanic spasms in both curarized and noncurarized patients was considered good. While maintenance of adequate arterial blood gases was often laborious, hypoxia was infrequently considered a cause of death. Cardiac standstill occurring up to four weeks after admission in patients who seemingly were doing well and usually had no evidence of arrythmia except sinus tachycardia was the commonest cause of fatality. One addict with recurrent tetanus, however, experienced three cardiac arrests and survived without sequelae.

Nonprotective levels of tetanus antibody were measured in a group of addicted patients. An extensive immunization program was conducted by nurse epidemiologists throughout the hospital and especially among clients of the addiction treatment programs.

Conclusion

This presentation has focused on the neurological findings observed in heroin addicts. The social and therapeutic aspects of addiction must not be overlooked.[44] Treating the overdosed patient or the patient who has an interesting neurological complication is totally insufficient if it is not coupled with simultaneous concern to ensure adequate rehabilitation and restoration. The need of the addict to recognize his intrinsic potential as a human being has been emphasized increasingly. In response to this recognition and to the desire on the part of an addict for help,

a responsibility falls on all health professionals to provide the necessary avenues of treatment in all dimensions—social and rehabilitative as well as medical. We can no longer ignore this broad responsibility.

This responsibility is all the more crucial in a community such as Harlem, where addiction to heroin and its complications contribute such a large component to other medical illnesses. The neurology service staff cooperates actively with the various programs of treatment and rehabilitation for heroin addicts, including the Methadone Maintenance Program. Group meetings are held that utilize, among other techniques, peer-group counseling. From the humane standpoint alone, it is necessary to prevent further exposure to the heroin-quinine adulterant mixtures which may precipitate neural disability. Patients who are addicts must be referred to a suitable treatment facility prior to discharge from the hospital for their acute illness. Over-all results are still limited, but evidence indicates that recovery from addiction is possible. An example is a heroin-addicted patient who was treated successfully for tetanus. His recovery was so complete that he became an oxygen therapist in the very recovery room where he himself had been a patient.

Since addiction to heroin is a major health problem in the community, further support must be given for establishment of truly community-based and community-oriented programs of prevention, education, and treatment. Active research programs defining the basic mechanisms in the addictive states must accompany various therapeutic approaches.

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